

## Antibiotic prophylaxis in patients with cirrhosis: Current evidence for clinical practice

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### Abstract

Patients with cirrhosis show an increased susceptibility to infection due to disease-related immune-dysfunction. Bacterial infection therefore represents a common, often detrimental event in patients with advanced liver disease, since it can worsen portal hypertension and impair the function of hepatic and extra-hepatic organs. Among pharmacological strategies to prevent infection, antibiotic prophylaxis remains the first-choice, especially in high-risk groups, such as patients with acute variceal bleeding, low ascitic fluid proteins, and prior episodes of spontaneous bacterial peritonitis. Nevertheless, antibiotic prophylaxis has to deal with the changing bacterial epidemiology in cirrhosis, with increased rates of gram-positive bacteria and multidrug resistant rods, warnings about quinolones-related side effects, and low prescription adherence. Short-term antibiotic prophylaxis is applied in many other settings during hospitalization, such as before interventional or surgical procedures, but often without knowledge of local bacterial epidemiology and without strict adherence to antimicrobial stewardship. This paper offers a detailed overview on the application of antibiotic prophylaxis in cirrhosis, according to the current evidence.

**Key Words:** Cirrhosis; Quinolones; Spontaneous bacterial peritonitis; Liver transplantation; Trans-jugular intrahepatic portosystemic shunt; Variceal bleeding

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**Core Tip:** Antibiotic prophylaxis represents a cornerstone for the management of several complications of decompensated cirrhosis, as spontaneous bacterial peritonitis

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and variceal bleeding. Short-term antibiotic prophylaxis is often applied in many other settings during hospitalization of patients with cirrhosis, such as before interventional or surgical procedures, but often without knowledge of local bacterial epidemiology and without strict adherence to antimicrobial stewardship.

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## INTRODUCTION

Progress has been made on the pathogenetic and prognostic role of bacterial infection (BI) in many clinical settings of liver cirrhosis. Bacterial translocation from the intestinal lumen is now considered key factor for the development and worsening of portal hypertension[1]. Moreover, cirrhotic patients, especially at advanced disease stages, experience an impaired immune-surveillance, with reduced response to pathogens and a contemporary “exhausted” systemic inflammation[2]. Both the high susceptibility to BI and the exaggerated systemic response trigger hepatic and extra-hepatic organs dysfunction, favoring the development of acute-on-chronic liver failure [3], and a sudden worsening of portal hypertension. Therefore, it is not unusual that an episode of BI impairs the natural course of the disease, increasing morbidity, mortality, and the risk of drop-out from the liver transplantation (LT) waiting list[4-6].

The development of aggressive, tailored strategies against BI has become a cornerstone in several fields of hepatology. It has been demonstrated that every hour of inappropriate antibiotic use was associated with 1.9 higher odds of death in patients with cirrhosis and septic shock[7]. Therefore, a timely, adequate antibiotic stewardship, defined as the optimal selection, dosage, and duration of antimicrobial treatment, saves lives.

To date, among pharmacological options, antibiotic prophylaxis appears the most effective preventive measure[8]. Indeed, its wise use has improved prognosis in many settings, such as spontaneous bacterial peritonitis (SBP) or acute variceal bleeding (AVB), becoming standard of care[9].

Nevertheless, the wide and prolonged use of systemic antibiotics (not only for prophylaxis) has brought lights and shadows in cirrhosis. Indeed, there has been the spread of multidrug resistant (MDR) bacteria, a huge healthcare problem that involves many fields of medicine with significant heterogeneity and prevalence across countries and centers, but exerting a highly negative prognostic impact in the setting of decompensated cirrhosis[10]. Moreover, *Clostridioides difficile* infection has been increasingly seen in cirrhotic patients, with prolonged hospitalization and higher in-hospital mortality when compared with non-cirrhotic patients with similar burden of comorbidities[11-13]. Moreover, the onset of such infection raises an already known intestinal dysbiosis, whose prevalence aligns with the severity of liver dysfunction. This may increase the risk of a refractory infection or impair the effectiveness of several treatments, as fecal microbiota transplantation[14].

Several other issues, such as the optimal length of prophylaxis, the preferable antibiotic class to use, and potential drug-drug interactions, remain still unexplored areas. These factors may explain the relatively low adherence to antibiotic prophylaxis in some fields. In a recent survey from France[15], almost all physicians prescribed antibiotics during AVB or after an episode of SBP (97.7% and 94.8%, respectively), but 1 out of 4 did not adhere to primary prophylaxis of SBP, without significant differences between workplaces (general *vs* university hospitals). In a recently published paper from the United States, investigating potential harmful prescriptions in patients with cirrhosis[16], nearly half (48.0%) of the patients with prior SBP filled an antibiotic prescription for secondary prophylaxis, but only 8.8% consistently filled this prescription.

Apart from these areas, antibiotic prophylaxis may be applied in many other settings during hospitalization of patients with cirrhosis, such as before interventional or surgical procedures. Therefore, this paper offers a detailed overview on the

application of antibiotic prophylaxis in cirrhosis, according to current evidence.

## SEARCH METHODS

PubMed/Medline until December 2020 was searched in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses[17] to identify all relevant medical literature included under the following search text terms: (“cirrhosis” OR “liver cirrhosis”) AND (“antibiotic prophylaxis” OR “prophylaxis”) for each of the following items: SBP, variceal bleeding, gastric varices, radiofrequency ablation (RFA), trans arterial chemoembolization, endoscopic retrograde cholangiopancreatography, LT, acute liver failure, and alcoholic hepatitis. Only studies involving patients over 18 years of age and in the English language were included. In addition, a full manual search was performed of all relevant review articles and the retrieved original studies.

## SBP

According to current guidelines[9,18], primary prophylaxis should start in patients with Child-Pugh score  $\geq 9$  and serum bilirubin level  $\geq 3$  mg/dL, impaired renal function or hyponatremia, and ascitic fluid protein lower than 15 g/dL, in view of previous randomized controlled trials (RCTs)[19-21]. A meta-analysis published in 2012 on three studies confirmed the beneficial role of primary prophylaxis in preventing SBP but not in reducing mortality[22]. Recently, an updated Cochrane meta-analysis did not show any gain in survival, in either primary or secondary prophylaxis[23], but the studies were at high risk of bias. Meta-analysis further clarified that, currently, no antibiotic seemed to be superior to others[23,24].

Moreau *et al*[25] investigated the role of norfloxacin in Child-Pugh class C cirrhotic patients. In this RCT, 291 patients (95% without prior SBP) were included independently of ascitic fluid protein level and then randomized to norfloxacin (400 mg/d administered for 6 mo) *vs* placebo. The primary endpoint (*i.e.* 6-mo survival) was not different between cohorts, neither was the incidence of SBP. When LT was considered as a competing risk of death or survival, patients given norfloxacin and having low ascitic fluid proteins displayed a significantly better outcome (cumulative 6-mo probability of death: 15.5% *vs* 24.8%,  $P = 0.045$ ). Notably, patients on norfloxacin therapy were also at lower risk of developing BI, *gram-negative* BI, and MDR infections during therapy. That said, in clinical practice, primary prophylaxis seems to be reasonable for high-risk patients (*i.e.* those with low ascitic fluid proteins and advanced disease), especially if they are waiting for LT.

The rationale behind secondary prophylaxis is the high recurrence rate in patients who recover from SBP (69% within a year)[26]. In a seminal RCT, Ginés *et al*[27] demonstrated that norfloxacin (400 mg/d) decreased SBP recurrence to 20%[27]. As a consequence, current guidelines recommend secondary prophylaxis with norfloxacin (400 mg/d) until death or LT after the first episode of SBP[9,18]. Although the previously reported meta-analysis did not strongly support this measure, due to heterogeneity across studies and a high risk of bias[23], secondary prophylaxis is routinely adopted worldwide.

Nevertheless, clouds are still on the horizon, as well as grey areas in this field. First, it has been questioned whether fluoroquinolones, widely investigated in such patients due to their potential ability in reducing the translocation of *gram-negative* bacteria from the gut lumen, still remain the drugs of choice. Indeed, there has been a changing epidemiology of BI in cirrhosis from *gram-negative* to *gram-positive* rods (especially in hospitalized patients), with increasing prevalence of *Enterococci*. Therefore, quinolones effectiveness after hospital-acquired SBP or after MDR-related SBP appears unclear. Moreover, warnings about their metabolic and cardiovascular side effects were added to previously known effects on joints and nervous system. Apart from trimethoprim-sulfamethoxazole, which has been proposed as a possible second-line drug, or first-line choice in quinolones-intolerant patients[28], no effective alternatives have been available between systemic antibiotics; head-to-head comparisons between quinolones and other drug classes, even in specific settings, are urgently needed. The use of other molecules such as rifaximin, which is poorly absorbed in the gastrointestinal tract with high intraluminal levels and already used for prophylaxis of hepatic encephalopathy, is a promising alternative[29] and warrants further investigation through dedicated trials. Moreover, there is some concern about the possible increase in MDR organisms after long-term antibiotic use, but this has not been confirmed in recent studies[25,30].

Lastly, adherence to life-long therapy represents a major issue, as mentioned above. A recent multicenter RCT demonstrated non-inferiority of prophylaxis with ciprofloxacin 750 mg once a week when compared with norfloxacin 400 mg/d in terms of SBP occurrence in a relatively small group of patients with low ascitic fluid protein and previous history of SBP[31]. If these results can be confirmed, without determining increased incidence of MDR rods, this new antibiotic schedule may be of help in clinical practice. In summary, patients with cirrhosis at highest risk of SBP development may require primary antibiotic prophylaxis, especially when awaiting LT. Secondary prophylaxis is recommended in view of stronger supporting evidence. Until now, quinolones remain the drugs of choice.

## VARICEAL BLEEDING

The beneficial role of antibiotic prophylaxis has been widely demonstrated in patients with decompensated cirrhosis and AVB. The rationale behind antibiotic prophylaxis is that a relevant percentage of bleeding episodes can be due to infection-related worsening of portal hypertension and coagulopathy. Moreover, infection is a causative factor in early variceal rebleeding[32]. A meta-analysis of 12 RCTs, including 1241 patients, confirmed the beneficial role of antibiotic prophylaxis in terms of overall mortality, mortality from BIs, and overall incidence of BIs[33].

Two major issues have to be addressed in the AVB setting. First, whether one class of antibiotics could be considered more effective than the others. A RCT conducted by Fernández *et al*[34] showed that patients who received norfloxacin had a higher rate of BI than those receiving cephalosporin, quinolone resistance being a major cause of infection breakthrough in these patients. The abovementioned meta-analysis[33] did not show any superiority of a specific class of antibiotics over the others, since these were all superior to the placebo; nevertheless, the beneficial effect seemed to be more pronounced in trials using cephalosporins (relative risk: 0.16, 95% confidence interval: 0.05-0.48), followed by quinolones (relative risk: 0.27, 95% confidence interval: 0.18-0.39). Therefore, current Guidelines recommend the use of intravenous (i.v.) cephalosporins (*i.e.* ceftriaxone 1 gr/d) as the best prophylactic therapy in AVB[35,36]. In clinical practice, the choice also has to take into account local epidemiology, setting of bleeding (*i.e.* out- vs in-hospital bleeding), and patient's individual features [previous antibiotic therapy; previous known infections or colonization(s)].

Second, the need for universal prophylaxis. Data from a propensity-matched cohort of 381 patients with AVB[37] showed that Child-Pugh A patients had a negligible risk of infection (2% vs 1%) and mortality (2.5% vs 0.4%), regardless of prophylaxis. The risk of infection rose in Child-Pugh class B patients, being significantly different in those receiving prophylaxis (6% vs 14%), even if mortality did not change (5% vs 7%). Finally, antibiotics significantly reduced both BI (19% vs 39%) and mortality (35% vs 62%) in Child-Pugh C patients. Therefore, current guidelines advocate prospective studies to assess properly the effectiveness of antibiotic prophylaxis in compensated patients[35].

In the setting of elective variceal band ligation, antibiotic use is less common. The rationale behind prophylaxis is the risk of bacteremia, which occurs in 3%-6% of cases, but it becomes clinically relevant only in a minority. A recently published systematic review and meta-analysis investigated this topic including 1001 procedures in 587 patients from 19 studies[38]. Overall, the frequency of bacteremia was 17% and 6% after sclerosis and band ligation, respectively. Comparing elective vs emergency procedures, the authors showed a significant difference for sclerosis (13% vs 22.5%) but not for band ligation (7.6% vs 3.2%). In summary, data do not currently provide strong recommendations about routine antibiotic prophylaxis for elective variceal therapy[35, 39]. Few data are available on the effectiveness of antibiotic prophylaxis for elective fundal variceal obturation with cyanoacrylate. A study from China[40] showed that sepsis occurred with a relatively low frequency (0.64%), whereas the risk was four-fold higher in the emergency setting. A further prospective RCT from China, including 107 patients undergoing elective cyanoacrylate obturation, showed that 53 who received cefotiam 2 gr i.v. before endoscopy experienced a lower incidence of post-operative complications, even if differences on infectious complications were not exhaustively reported[41]. Finally, a small study from Thailand compared cyanoacrylate injection in urgent vs elective setting, showing a negligible rate of peri/post-procedural infectious episodes in the former group (0% vs 20%)[42].

In summary, antibiotic prophylaxis remains a cornerstone for decompensated cirrhosis with AVB. According to available data, its use may be not routinely used in

the non-urgent setting.

## INTERVENTIONAL PROCEDURES

Trans jugular intrahepatic portosystemic shunt (TIPS) has been increasingly adopted in patients with cirrhosis, especially for the treatment of refractory ascites and variceal bleeding. Sepsis or bacteremia are quite common complications of TIPS placement, occurring in 2%-10% of cases[43,44]. Stent infection (*i.e.* endotipsitis) is a rare condition, caused by either *gram-positive* or *gram-negative* bacteria and can occur early (*i.e.* within 3 mo) after stent placement, or in a later period[45,46]. A single-center randomized study on 105 patients showed a non-significant reduction of post-interventional infections (20% *vs* 14%) after prophylactic administration of cephalosporin (cefotiam, 2 g i.v.). At multivariate analysis, multiple stenting, maintenance of central venous line, but not severity of underlying liver disease, had a significant impact on post-TIPS infection[47]. The same group further demonstrated that different antibiotic dosages for prophylaxis (single dose of ceftriaxone, 1 gr *vs* 2 gr i.v.) were not associated with different outcomes in terms of post-procedural infections in 82 patients undergoing elective TIPS (2.6% BI occurrence within 1 wk, in both groups)[48]. That said, current guidelines do not suggest the routine use of antibiotic prophylaxis for TIPS placement[49,50], mainly because strong evidence for this is still lacking[51]. Nevertheless, this must be weighed against the risk of serious post-procedural septic events. Therefore, antibiotic prophylaxis may be considered at least for expected technically difficult procedures or in patients with previous biliary interventions.

Considering endotipsitis, there is no evidence for adopting long-term prophylaxis given the rarity of the condition and the absence of robust microbiological data. Lastly, it has been proposed that antibiotic prophylaxis may be considered in patients having a diagnosis of a thrombosed TIPS, before invasive procedures (*e.g.*, gastrointestinal endoscopy), but larger studies are needed to properly assess this[46].

Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used procedure for many benign and malignant diseases of the biliary tract. A systematic review of nine RCTs showed that antibiotic prophylaxis reduced bacteremia in patients undergoing elective ERCP, but in the subgroup of patients with uncomplicated ERCP, the effect of antibiotics was less pronounced[52]. Therefore, American guidelines recommend antibiotic prophylaxis for prevention of cholangitis in cases of biliary duct obstruction and incomplete drainage[53]. Endoscopic procedures in patients with primary sclerosing cholangitis fall in this special group, due to multiple strictures and frequent prevalence of bacteriobilia, therefore antibiotic prophylaxis is recommended[54,55].

RFA and trans-arterial chemoembolization (TACE) are interventional procedures for the treatment of hepatocellular carcinoma. RFA has been classified as a clean procedure in such patients, not requiring routine antibiotic administration[56]. The incidence of post-procedural abscess is equal to 0.8%, according to available case series [57,58].

Thermal ablation determines heat-induced coagulative necrosis of the tumor. Therefore, bacterial superinfection may be a quite common complication, due to bacterial colonization of the necrotic area; moreover, thermal injury can connect biliary ducts with the ablation zone, creating a route for contamination from enteric bacteria in patients with underlying altered biliary anatomy (*e.g.*, choledocho-jejunostomy, prior endoscopic sphincterotomy). Current evidence therefore suggests that antibiotic prophylaxis may be used in such patients[59-63].

The rationale of TACE is to reduce arterial feeding to a malignant nodule, adding local chemotherapy, such as doxorubicin. A recent retrospective, single-center study from the United States analyzing the outcome of 171 patients who underwent 253 TACE without antibiotic prophylaxis[64] reported no infectious complications. A meta-analysis on four studies reported no significant difference between patients undergoing antibiotic prophylaxis and patients without[65], but interventional techniques were not homogeneous across studies and some endpoints (*e.g.*, post-procedural fever) may unmask inflammatory response rather than true infectious complications. Local instillation of antibiotic particles during interventional procedures has recently been proposed[66] but requires further investigations.

Yttrium<sup>90</sup> embolization is a relatively novel interventional technique for the treatment of hepatocellular carcinoma or liver metastases. Few data are currently available about antibiotic prophylaxis in this setting, also in view of heterogeneous patients' characteristics, such as presence or absence of cirrhosis. A recently published

survey from 45 European centers confirmed different strategies regarding antibiotic prophylaxis, which was routinely adopted in 8% of cases[67]. However, as for chemoembolization, patients with a history of biliary endoscopic or surgical interventions seemed to be those who may receive antibiotic prophylaxis[68].

In summary, antibiotic prophylaxis is not routinely recommended for elective interventional procedures in patients with cirrhosis. It should be carefully considered in high-risk patients, such as those with bilio-enteric anastomosis, whereas it should be routinely adopted in patients with primary sclerosing cholangitis undergoing ERCP.

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## LT

Infection remains a major cause of morbidity and mortality in liver transplant recipients, with a significant burden on short-term post-operative graft and patient survival. Length of surgery, prior transplant or abdominal surgery, severity of liver disease at time of transplantation, and post-operative complications represent the most important risk factors for post-LT surgical site infection (SSI). The pathogens most commonly associated with early SSIs are *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Acinetobacter*, but also *Enterococci*[69,70].

Theoretically, the main role of pre-operative prophylaxis would be to prevent SSI. Although a Cochrane meta-analysis, after including only one RCT (at high risk of bias), concluded that benefits and harms of prophylactic regimens were difficult to assess[71]; antibiotic prophylaxis has been widely used before LT, being justified by high infection rates (even during ongoing prophylaxis) and complexity of surgery.

Data on the type and length of peri-operative LT prophylaxis are scant. In a survey from 61 European LT centers, Vandecasteele *et al*[72] reported that the type of antibiotic prophylaxis was heterogeneously chosen among centers. An extended spectrum antibiotic regimen was reported in the majority of cases (73%) for elective LT. Notably, 25% centers reported a change in prophylactic schedule (in terms of drug class and length) for the sickest candidates (*i.e.* those with acute-on-chronic liver failure). The survey further demonstrated that one-third of centers used to change antibiotic prophylaxis in the presence of LT for candidates with acute liver failure (ALF).

Current American guidelines recommend the use of piperacillin-tazobactam, or cefotaxime plus ampicillin as routine prophylaxis during LT[73], considering cefuroxime, metronidazole, clindamycin, or quinolones as important alternatives in candidates with allergy to B-lactams. Notably, the guidelines highlight correct timing of prophylaxis (60 min before surgical incision for most antibiotics) and the need to repeat the dose in cases of prolonged surgery and suggest against the routine use of vancomycin, since it may increase the risk of post-transplant MDR rods. Pre-transplant surveillance for ruling-out colonization(s), as well as updates on local bacterial epidemiology, represent further important measures for tailoring prophylaxis to prevent antibiotic failure and reduce MDR development[74,75]. The length of antibiotic prophylaxis remains debated, with heterogeneous courses ranging from 24 h to 5 d. Recently, a RCT from the United States compared short-course (*i.e.* intraoperative doses) and 72-h extended course in 97 adult LT recipients[76]. The authors did not find any difference in prevalence of SSI (19% *vs* 27%) or overall infection (35% *vs* 37%) between groups, providing evidence in favor of a shorter antibiotic schedule. Larger studies are warranted to confirm properly these hypotheses. Recently, antibiotics have been investigated as factors potentially changing post-surgical ischemia-reperfusion injury. In mice, antibiotics prior to LT reduced the gut microbiota, decreasing the inflammatory response and promoting homeostatic responses[77]. These data were confirmed in a retrospective group of LT recipients, confirming that pretreatment with antibiotics was associated with improved hepatocellular function and a decreased incidence of early allograft dysfunction. Further data are needed to confirm properly the effectiveness of antibiotic therapy in LT recipients, beyond its preventive role against SSI.

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## SPECIAL CONDITIONS

### **Severe alcoholic hepatitis**

Patients with severe alcoholic hepatitis (sAH) are prone to develop infection due to their severe state of immunosuppression[78]. BI accounts for nearly 80% of overall

invasive infections, although growing attention has been paid to fungal infection, especially Aspergillosis. The prevalence of BI at hospital admission and during hospitalization is up to 30% and 60%, respectively[79,80]. Urinary tract and airways are the most common infectious sites in such a cohort, the latter being highly prevalent after corticosteroid treatment, probably due to an increasing need for mechanical ventilation and intensive care management.

Corticosteroid therapy has been proven effective in improving short-term survival in sAH and currently represents the first-choice medical therapy.

Given the high prevalence of BI at baseline, and the theoretical immunosuppressive role of corticosteroids, several studies investigated whether they would increase infectious risk, and whether infection occurring during corticosteroid therapy would significantly impair survival[81]. A study on a large cohort of patients with sAH confirmed an increasing rate of BI during corticosteroid treatment (23% *vs* 12% at baseline)[82], but the actual role of corticosteroids was difficult to ascertain. Considering prognosis, a landmark study from France[79] demonstrated that the probability of being infected after/during corticosteroids reduced the survival benefit given by medical therapy. A further meta-analysis on 12 studies involving 1062 patients did not show a higher short-term risk of death for infection in those receiving corticosteroids, when compared with those receiving a placebo[83].

That said, antibiotic prophylaxis has been proposed in such a setting. Vergis *et al*[82] demonstrated that an infection occurring prior to corticosteroid introduction has a more favorable course if the antibiotic is continued also during steroid therapy. Moreover, the use of prophylactic antibiotics (prescribed in 45% of cases) was associated with a lower risk of death than that in patients who did not receive prophylactic antibiotics (13% *vs* 52%)[82]. Summarizing the available data, infection is highly prevalent in patients with sAH, both in those receiving steroids and not. The impact of steroids as a potential risk factor for infection is currently debated and not supported by robust data. An ongoing clinical trial (NCT02281929) assessing the prophylactic role of amoxicillin-clavulanic acid will probably clarify this point.

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## ALF

In a similar fashion to sAH and acute-on-chronic liver failure, ALF is characterized by a severe state of immunosuppression. Moreover, the rapidly evolving scenario of ALF, including the changing neurological status and need for circulatory support and mechanical ventilation, makes diagnosis of BI even more difficult. The prevalence of BI is nearly 30%-34%, according to recent studies[84,85]. Severity of the underlying condition and presence of cerebral edema seem to be associated with infection development. Occurrence of infection is obviously associated with worse outcome in ALF, since it may further derange hepatic and extra-hepatic organ(s) failure and may delay or contra-indicate LT. Recently, a retrospective analysis of a large United States cohort by Karvellas *et al*[86] did not show any significant improvement with administration of antibiotic prophylaxis in 600 patients with ALF, if compared with the 951 patients who did not receive antibiotics. Indeed, there was no significant difference in the probability of having bloodstream infection based on receiving prophylaxis (12.8%) or not (15.7%  $P = 0.12$ ). Notably, the timing of prophylaxis was not homogeneous, nor were the clinical characteristics between cohorts, such as type of prophylaxis (47% extended spectrum beta-lactam, 39% vancomycin, 27% fluoroquinolones, and 20% third and fourth generation cephalosporins). Other strategies, such as selective bowel decontamination, did not show any significant benefit either [87]. In summary, current guidelines say that, even the routine use of prophylactic antibiotics does not increase survival in such patients, a strict surveillance for infection should be provided in order to start antibiotic therapy as early as possible[88,89]. Prophylaxis should be considered in cases where illness progression is considered likely, as in those with worsening encephalopathy, signs of systemic inflammation, or awaiting LT[90,91]. The choice of antibiotic class is even more debated, probably due to heterogeneous epidemiology across studies and the relevant number of culture-negative infections. That said, the high prevalence of pneumonia[87], as well as the presence of indwelling catheters and invasive procedures should be taken into account.

**Table 1** Current recommendations and uncertainties regarding antibiotic prophylaxis in patients with cirrhosis

Procedure/clinical setting	Antibiotic prophylaxis	Areas of uncertainties
Spontaneous bacterial peritonitis	Primary prophylaxis recommended in decompensated patients with low ascitic fluid proteins. Secondary prophylaxis recommended	Second-line antibiotics. Quinolone resistance. Rifaximin. Secondary prophylaxis after MDR infection
Variceal bleeding	Prophylaxis recommended in acute bleeding from esophageal/gastric variceal bleeding	Prophylaxis in compensated ( <i>e.g.</i> , Child-Pugh A) patients having acute variceal bleeding. Prophylaxis in elective endoscopic therapy of gastric/esophageal varices
Endoscopic retrograde cholangiopancreatography	Routine prophylaxis not recommended. Prophylaxis is recommended in patients with incomplete drainage and in those with primary sclerosing cholangitis	
Transjugular intrahepatic portosystemic shunt	Prophylaxis should be considered in difficult procedures	Prophylaxis in patients with thrombosed transjugular intrahepatic portosystemic shunt undergoing invasive procedures
Radiofrequency ablation. Trans-arterial chemoembolization. Radioembolization	Routine prophylaxis not recommended. Advisable in patients with prior interventions on biliary tree	Intra-procedural antibiotic instillation
Liver transplantation	Routine prophylaxis is recommended	Length of prophylaxis
Severe alcoholic hepatitis receiving steroids	Prophylaxis would be preferable	Length of prophylaxis, antibiotic class
Acute liver failure	Prophylaxis is advisable in high-risk patients, or those waiting for liver transplant	Antibiotic class

## CONCLUSION

BI represents a common complication in patients with cirrhosis due to disease-related immune dysfunction. In this setting, antibiotic prophylaxis plays a major role, especially in high-risk patients. Type and length of prophylaxis are supported by low quality data in several fields of hepatology and LT (Table 1) and are currently heterogeneously adopted across centers. Since unnecessary prophylaxis or prolonged schedules may increase the risk of anaphylaxis and development of MDR rods, a wise adherence to current recommendations and a rigorous application of antibiotic stewardship are of utmost importance. Other important remarks should be offered to the reader. First, this paper does not include prophylaxis against invasive fungal infection, which is another serious complication in cirrhosis, having an increasing prevalence and a dreadful outcome[92]. Second, although we have focused on systemic antibiotic prophylaxis, growing evidence on non-antibiotic prophylaxis against BI in cirrhosis has to be mentioned. The role of rifaximin, a nonabsorbable antibiotic, has been largely demonstrated for patients with prior episodes of hepatic encephalopathy. Other emerging selective gut decontamination modalities, including prebiotics and probiotics, and fecal microbiota transplant are in the pipeline[93]. Future studies are therefore warranted to investigate whether these modifications to gut microbiota will reduce the occurrence of BI (especially SBP), acting as prophylactic strategies. Moreover, the preventive role of non-selective beta blockers and albumin has to be robustly confirmed, according to underlying liver function and setting[94,95].

Finally, we strongly encourage an updated review of local bacterial epidemiology in clinical practice, and a strong liaison with infectious disease specialists, pharmacologists, microbiologists, and epidemiologists, in order to use tailored prophylaxis regimens, because the right prevention works better than a cure.

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